Drawings

The Examiner's maintenance of the objections to the drawings is acknowledged. Formal drawings will be filed after receipt of a Notice of Allowance.

Objections to Informalities

Claim 1 was objected to because of duplication of the word "from" in claim lines 6-8. Claim 1 has been amended to overcome this objection

Rejections Under 35 U.S.C. 112, First Paragraph

Claims 1, 4-9, and 23-27 stand rejected under 35 U.S.C. 112, first paragraph, on the ground that the specification lacks support for the phrase "beginning at the completion of." Specifically, the Examiner believes that the passages cited by Applicant as supporting this phrase, namely page 5, lines 30-32, page 6, lines 10-14, and Figure 8, do not provide support for phases beginning at the completion of previous phases. The rejection is respectfully traversed.

Applicants respectfully point out that *ipsis verbis* support is not required and that whether the support is sufficient must be considered from the point of view of one skilled in the art. Page 5, lines 30-32 of the specification states: "The microspheres of the instant invention release the antigen and/or adjuvant in three phases: an initial burst, a slow release, and a second burst." From this sentence, one skilled in the art would understand that the release profile for the microspheres can be divided into three phases. One skilled in the art would also understand, in the absence of any contrary teachings, that the second phase begins at the completion of the first phase and that the third phase begins at the completion of the second. This notion is inherent in description of a release profile characterized by three phases. Page 6, lines 10-14 confirms this interpretation, stating that "antigen is released from the microspheres in a triphasic pattern." This passage also explicitly states that antigen is released in the "second burst [i.e., the third phase]

after" the period corresponding to the second phase. Figure 8 shows three distinct phases of release: an initial burst, a slow release, and a second burst. Moreover, Figure 8 shows that the slow release (second phase) begins immediately after the initial burst (first phase) and that the second burst (third phase) begins immediately after the period of slow release (second phase).

The Examiner contends that "although Figure 8 depicts the % release, there is no clear indication where the phases begin and end as recited in the claims." Office Action, at 3. Applicants respectfully submit that one skilled in the art would not take the same view of Figure 8, especially when considered in the context of the specification's description of triphasic release. The specification indicates that the first phase is an initial burst. One skilled in the art studying Figure 8 would conclude that the initial burst ends after about 2 days of release because the percent cumulative release jumps to 20% in the first two days of release and then abruptly levels off. A gradual increase in percent cumulative release continues from after the initial burst until about day 30, defining the second phase of slow release. A sharp increase in the slope of the percent cumulative release curve at about day 30 indicates the end of the slow release (second) phase and the beginning of the third phase, in which the second burst of release occurs. Thus, one skilled in the art would readily appreciate that Figure 8 illustrates the triphasic release profile recited in the claims. Applicants respectfully remind the Examiner that the figures are as much a part of the disclosure as the written description, and Applicants are therefore entitled to rely on the figures as support for claim language.

Claims 1, 4-9, and 23-27 were rejected under 35 U.S.C. 112, first paragraph, on the ground that the specification lacks support for the use of an aqueous antigen concentration of less than 1 milliliter (mL) per 3 grams (gm) of polymer. This rejection is respectfully traversed as such support is found in the specification at least at page 16, line 29 to page 17, line 8. This passage indicates that the preferred polymer concentration is 0.3 gm/mL to 0.6 gm/mL or 3-6 gm/10 mL. As described in the Preliminary Amendment at page 5, the specification discloses an emulsion containing 10 mL organic polymer solution for each 1 mL of aqueous antigen. Thus, the specification clearly indicates that preferred emulsions contain 3-6 gm of polymer for each mL of antigen. This represents an antigen concentration ranging from 1 mL antigen per 3 gm polymer to 1 mL antigen per 6 gm polymer. The latter is equivalent to 0.5 mL

antigen per 3 gm polymer. As 0.5 is less than 1, the specification provides clear support for antigen concentrations less than 1 mL antigen per 3 gm polymer.

The 112, first paragraph rejection was also based on the Examiner's view that the specification failed to provide support for a first phase of release "over a period of about 1 to 2 days," as recited in Claim 1. The support for this claim element is as discussed above.

Because the specification fully supports the language of the pending claims, withdrawal of the 112, first paragraph rejection is respectfully requested.

Rejection Under 35 U.S.C. 112, Second Paragraph

Claims 1, 4-9, and 23-27 were additionally rejected under 35 U.S.C. 112, second paragraph, as indefinite. The Examiner believes that Claim 1 is indefinite for failure to recite a lower limit for the antigen concentration. Applicants submit that Claim 1 is clear and definite in this regard and therefore respectfully traverse the rejection. The claim recites that antigen is present in the recited emulsion. One skilled in the art therefore understands that the claimed invention includes microspheres derived from an emulsion including some aqueous antigen, provided the microspheres meet all other claim terms. One skilled in the art knows when he prepares an emulsion including antigen and would therefore have no difficulty recognizing when he is practicing the claimed invention. Because the metes and bounds of the claims are clear, withdrawal of the 112, second paragraph rejection is respectfully requested.

Rejections Under 35 U.S.C. 103

Sanders et al., Eldridge et al., and Jeffery et al.

Claims 1, 4, 9, and 23-27 stand rejected under 35 U.S.C. 103 as unpatentable over Sanders et al., J. Pharmaceutical Sciences 73:1294-97 (1984) ("Sanders"), in view of Eldridge et

al., Mol. Immunol. 28:287-94 (1991) ("Eldridge"), and further in view of Jeffery et al., Pharmaceutical Research 10:362-68 (1993). The rejection is respectfully traversed.

Applicants pointed out in the Preliminary Amendment filed February 22, 1999, that "Sanders lacks credible data regarding release rates." For this reason, Sanders fails to teach triphasic release wherein specific percentages of an agent are released during specific phases of release. Applicants further pointed out that neither Eldridge nor Jeffery disclose triphasic release from a single microsphere population. In response, the Examiner noted that "one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references." Office Action, at 4. Applicants agree with this point, but disagree that it has any bearing on Applicants' statements in the Preliminary Amendment. Applicants discussed the references individually, as is standard, but Applicants' statement that "[n]either Eldridge nor Jeffery remedy the deficiencies of Sanders" makes it clear that Applicants' remarks were directed to the combination of references. *See* Preliminary Amendment, at 12. Furthermore, Applicants concluded that "Sanders, Eldridge, and Jeffery, taken singly or together, fail to teach or suggest the combination of elements recited in the pending claims." Preliminary Amendment, at 13.

The Examiner believes that Sanders teaches a triphasic release profile based on Sanders' disclosure of a formulation containing a 69:31 PLGA copolymer, which was tested in the rat estrus suppression model. This data appears in Figure 4, which indicates that "[e]strus suppression profiles," are depicted therein. As Sanders clearly acknowledges (page 1296, col. 1), estrus suppression profiles are not equivalent to release profiles. Estrus suppression profiles, for example, provide no indication of percent cumulative release over the period of release. Such profiles therefore provide no indication of the percent release over a given portion of the period of release.

Claim 1, the only pending independent claim, recites that about 0.5 to 30 percent of the antigen is released from the microspheres over a period of about 1 to 2 days. Figure 4 of Sanders indicates that the 69:31 PLGA copolymer formulation suppressed estrus in most of the rats to which it was administered for about 12 days. These data do not indicate the amount of

active agent released over about 1 to 2 days. Claim 1 further recites that, after about 1 to 2 days, "less than 10 percent of the antigen is released from the microspheres over a period ranging from about 30 to about 180 days." Sanders' Figure 4 shows that over this period, estrus is suppressed in most animals from until about day 12, not suppressed in any animal from about days 12-19, suppressed in some animals from about days 20-29, not suppressed in any animal from about days 30-37, suppressed in an increasing number of animals from about days 38-41, and suppressed in all animals from about days 42-85. This complex profile provides no teaching or suggestion of Claim 1's second phase, "wherein less than 10 percent of antigen is release from the microspheres over a period ranging from about 30 to about 180 days" or Claim 1's third phase "wherein the remaining antigen is released from the microspheres over a period ranging from about 10 to 30 days."

These points are the basis for Applicants' statements in the Preliminary Amendment that Sanders lacks credible data regarding release rates and thus does not teach or suggest triphasic release within the meaning of Claim 1. The Examiner countered this point by contending that "the claims do not recite the release rate." Office Action, page 5. However, Applicants were using "release rate" to denote an amount of release per unit time, specifically per phase of release. The claims clearly recite the amount of release in each phase: about 0.5-30% in the first phase, less than 10% in the second phase, and the remaining antigen (about 40-99.5%) in the third phase.

Neither Sanders, nor Eldridge, nor Jeffery teach or suggest a triphase release profile in which the recited amounts of antigen are released over the recited time periods. Neither Sanders, nor Eldridge, nor Jeffery suggest the desirability of this release profile or how to achieve it. Eldridge's only teaching regarding the possibility of multiphasic release suggests that two populations having different copolymer ratios or different microsphere sizes could be blended. Eldridge, at 290, col. 1. Jeffery is devoid of any teaching regarding multiphasic release.

In response to Applicants' point regarding Eldridge's blended populations, the Examiner noted that the claims do not recite "non-blended." However, the Examiner overlooks

Claim 1's recitation of a population of microspheres that "is produced from an emulsion comprising aqueous antigen and a polylactide or PLGA polymer." Such a population necessarily shares common properties, some of which are explicitly recited in Claim 1 (i.e., all microspheres produced from the emulsion are derived from polymer having a given lactide:glycolide ratio and inherent viscosity). Claim 1 also recites that "the microspheres have an antigen release profile characterized by three phases." This language makes it clear that the microspheres are an essentially homogenous (i.e., a non-blended) population in that they share a common triphasic release profile.

Eldridge's discussion of achieving multiphasic release using blended populations evidences that achieving any desired multiphasic release profile with a homogenous population was not, as the Examiner appears to believe, within the level of skill in the art. If it was, Eldridge surely would have discussed it. The notion that any multiphasic release profile could be achieved using a single population of microspheres was similarly absent from the comprehensive chapter entitled "Design of Biodegradable Polymer Systems for Controlled Release of Bioactive Agents" by Floy et al. (in Polymeric Delivery Systems: Properties and Applications [American Chemical Society, Washington, D.C., 1993]) which has been cited by the Examiner. Floy states "[r]elease profile possibilities can be expanded by employing mixtures of two or more polymers ." Floy, at 157. Floy further cautions that "this approach adds additional complexity to ***an already complex system.***" *Id.* (emphasis added).

Applicants believe that the Examiner is giving insufficient weight to the acknowledged complexity of polylactide/PLGA polymeric release systems. The rejection appears to based solely on the Examiner's view that it was known that various parameters altered various release characteristics. But the Examiner has cited no art indicating that the ways in which variations in these ***multiple*** parameters ***interacted*** to affect release profile was understood. The specification identifies the following parameters and demonstrates how they interact to affect encapsulation efficiency and release profiles: temperature during encapsulation (page 33, line 13 - page 34, line 26), amount of solvent in the second emulsion prior to polymer addition (page 34, line 1 - page 35, line 3), viscosity of the polymer phase (page 35, line 27 - page 36, line 16), ratio of the aqueous to organic volumes in the first emulsion (page 35, lines 26-31),

polymer molecular weight and copolymer ratio (page 37, line 31 - page 38, line 10), polymer concentration, (page 38, line 11 - page 39, line 8), mixing speed (page 40, lines 28-33), and drying method and time (page 41, line 39 - page 45, line 36). To arrive at a given triphasic release profile, one would have had to know (or be able to determine, without undue experimentation) how the interaction of these 10 parameters affected the amount of agent release in the initial burst, the duration of an intermediate period of low release, and the amount of agent released in the second burst as well as the duration of this release. Nothing in the art cited by the Examiner indicates that PLGA systems were this well understood.

Moreover, the Examiner has failed to identify any specific motivation for producing microspheres having the claimed release profile. The case law establishes that the motivation to produce the invention must withstand rigorous scrutiny. The Federal Circuit's discussion of this requirement in *In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998) is instructive. There, the court stated:

> "[V]irtually all [inventions] are combinations of old elements." *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 698, 218 U.S.P.Q. 865, 870 (Fed. Cir. 1983); *see also Richdel, Inc. v. Sunspool Corp.*, 714 F.2d 1573, 1579-80, 219 U.S. P.Q. 8, 12 (Fed. Cir. 1983) ("Most, if not all, inventions are combinations and mostly of old elements."). Therefore an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be "an illogical and inappropriate process by which to determine patentability." *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570, 38 U.S.P.Q. 2d 1551, 1554 (Fed. Cir. 1996).
>
> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness.

Id. at 1357. The court then noted that the Board had failed to "explain what ***specific*** understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested" the invention *Id.* (emphasis added). Finding that the Board had "merely invoked the high level of skill in the . . . art," the court stated:

> If such a rote invocation could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technical advance. Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection. To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.

Id. at 1357-1358.

Applicants submit that, in the present case, the Examiner is invoking the knowledge in the art of parameters affecting release profiles and has failed to identify the "***specific*** understanding or technological principle within the knowledge of one of ordinary skill in the art" that would lead to the ***specific*** release profile claimed. See *id.* at 1857. Accordingly, the Examiner has not cited sufficient motivation to support a case of *prima facie* obviousness. Because the cited references provide neither motivation nor means for producing the claimed compositions, withdrawal of the rejection is respectfully requested.

Sanders et al., Eldridge et al., Jeffery et al., and Wang et al.

Claims 5-7 are rejected under 35 U.S.C. 103 as unpatentable over Sanders, Eldridge, Jeffery, and Wang et al., J. Controlled Release 17:23-32 (1991). The rejection is respectfully traversed.

Claims 5-7 depend, directly or indirectly, from Claim 1 and relate to compositions comprising adjurant. The Examiner relies on Wang solely for its teaching of including an adjuvant in PLGA microspheres, acknowledging that "Wang et al is not directed to triphasic

release." Office Action, at 6. Thus, Wang fails to provide any suggestion of microspheres have the claimed triphasic release profile recited in Claim 1, much less any indication of how to produce them. As Sanders, Eldridge, and Jeffery are similarly deficient, Claims 5-7 are patentable over the cited combination. Withdrawal of the rejection is therefore respectfully requested.

Sanders et al., Eldridge et al., Jeffery et al., Wang et al., and Newman et al.

Claim 8 is rejected under 35 U.S.C. 103 as unpatentable over Sanders, Eldridge, Jeffery, Wang, and Newman et al, AIDS Research and Human Retroviruses 8:1413-18 (1992). The rejection is respectfully traversed. Claim 8 depends ultimately from Claim 1 and recites that the microspheres comprise QS21 adjuvant. Newman is cited solely for its teaching of QS21 as an adjuvant and does nothing to remedy the above-discussed deficiencies of Sanders, Eldridge, Jeffery, and Wang. Withdrawal of the rejection is therefore respectfully requested.

Floy et al.

The Examiner rejected Claims 1, 4, 9, and 23-27 under 35 U.S.C. 103 as upatentable over Floy et al. (*supra*). The Examiner stated:

> Floy et al teach [that] drug release profiles from [PLGA] . . . microspheres typically exhibit a triphasic release pattern. This pattern is characterized by an initial, rapid release of the encapsulated compound during the first few days. A latent period then occurs where little of the compound is released. The latent period is then followed by a major phase of drug release.

Office Action, at 9. The Examiner acknowledged that "Floy et al do not teach the specific ranges recited in the claims." *Id.* However, the Examiner stated that "[w]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *Id.* The rejection is respectfully traversed.

The rejection is based on the Examiner's view that the release profile recited in Claim 1 represents mere optimization. This view, however, ignores the large number of parameters that affect release from polylactide/PLGA polymers and the art-recognized complexity of their interactions. This complexity is evidenced by Floy's explicit characterization as PLGA drug delivery as a "complex system." Floy, at 157.

Furthermore, none of the cited references teach or suggest exploiting the triphasic release of polylactide/PLGA systems as Applicants have done. The references establish that workers in the field were focused primarily on continuous release systems. Floy reflects this focus, stating:

> Controlled delivery eliminates the "peak and valley" effects observed with frequent, pulsatile administration of traditional parenteral systems. The widely varying plasma levels can result in the development of undesirable side effects at peak plasma levels while periods of insufficient treatment may occur at trough levels. Therefore, controlled release delivery systems, in theory, can result in better drug utilization by ***delivering the drug at a desired rate resulting in a narrower range of plasma levels.***

Floy, at 155 (emphasis added). Floy goes on to discuss agents with a narrow therapeutic index, noting that "[l]ittle or no initial burst of drug from the delivery system is a strict requirement." *Id.*

The only teachings regarding multiphasic release in the cited references suggest only that it might be possible to achieve desired profiles by blending mixtures of two or more polymers. Eldridge, at 290, col. 1; Floy, at 157. However, Floy's statement that blending "adds additional complexity to an already complex system" indicates that this strategy is not necessarily straightforward. See *id.* Applicants' strategy of manipulating at least 10 different parameters to produce a microsphere population having a desired multiphasic release profile is not even remotely contemplated in any of the cited references. The only motivation for such an approach is found in Applicants' specification.

The Examiner states:

> [I]t would have been obvious to one of ordinary skill in the art at the time the invention was made to encapsulate antigens within microspheres of various diameters, compositions, and viscosity in order to deliver the antigen for release in various amounts and at various duration[s], absent evidence to the contrary or unexpected results.

Office Action, at 9. This statement ignores the process conditions and other parameters discussed above that Applicants have shown affect release profiles.

Moreover, the very generality of this statement demonstrates that the rejection rests on references that, at best, invite random experimentation "to deliver the antigen for release in ***various*** amounts and at ***various*** durations." Applicants fail to see how such a position can be reconciled with recent Federal Circuit precedent that requires the Patent Office to "explain what ***specific*** understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested" the invention. *In re Rouffet*, at 1357 (emphasis added). Because the cited references lack any disclosure regarding the desirability of the specific release profile recited in Claim 1, much less any adequate teaching of how to achieve it, Applicants submit that the pending claims are patentable over Floy. Withdrawal of the rejection of Claims 1, 4, 9, and 23-27 is therefore respectfully requested.

Floy et al. and Immunization Practices Advisory Committee Recommendations

The Examiner rejected Claims 5-7 under 35 U.S.C. 103 as unpatentable over Floy in view of Immunization Advisory Committee, Clin. Pharm. 8:839-851 (1989) ("the IAC recommendations"). The rejection is respectfully traversed. The IAC recommendations are cited solely for the proposition that "adjuvants can be administered with antigens in order to enhance an immune response." Office Action, at 10. The IAC recommendations outline the benefits, costs, and risks of immunization against infections diseases in the United States and make recommendations for immunization based thereon. This reference neither teaches nor suggests the claimed triphasic release profile, nor does it provide any motivation or means for producing

polymeric microspheres with such a release profile. Because the IAC recommendations fail to remedy the deficiencies of Floy, Claims 5-7 are clearly patentable over the cited combination. Withdrawal of the rejection is therefore respectfully requested.

Floy et al., Immunization Practices Advisory Committee Recommendations, and Newman et al.

The Examiner rejected Claim 8 under 35 U.S.C. 103 as unpatentable over Floy, in view of the IAC recommendations, and further in view of Newman. The rejection is respectfully traversed. As discussed above, Newman is cited solely for its disclosure of the QS21 adjuvant. Because Newman is devoid of any teaching or suggestion of triphasic release, much less the specific triphasic release profile recited in the claims, Newman fails to supply the teachings missing from Floy and the IAC recommendations. Accordingly, Claim 8 is patentable over the cited combination, and withdrawal of the rejection is therefore respectfully requested.

Conclusion

As Applicants respectfully submit that the application is now in condition for allowance, a notice of allowance is respectfully requested. If the Examiner has any questions regarding this submission, the Examiner respectfully requested to telephone and confer with undersigned attorney at (640) 849-4910. Furthermore, in the interest of expediting prosecution, an examiner interview is requested in the event that the Examiner believes that this submission does not place the application in condition for allowance.

Respectfully submitted,

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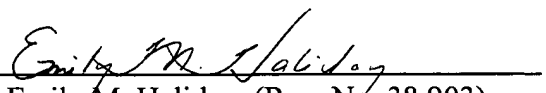
Dated: July 19, 1999

By: 

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